REMARKS

Reconsideration is respectfully requested in view of the remarks which follow.

The claims presently pending in the subject application are 26 – 43 and 47 – 49.

Claims 26 – 43 and 47 – 49 stand rejected under 35 USC § 103(a) over Alt, U.S. 5,512,684 in view of Gandolfi et al (US 4,999,362) and in view of Dorwald (Side Reactions in Organic Synthesis 2005, Wiley-VCH, page 2). This rejection is respectfully traversed.

Applicants respectfully disagree with the Examiner's reasoning and submit further arguments in support of the non-obviousness of the pending claims. As a matter of fact, the Examiner in the previous Office Actions has already used Alt US '684 (and its equivalent US '416) as a reference in order to support his obviousness rejections. Such rejections have previously been overcome. The last rejection introduced a new reference (Gandolfi) to be combined, but ultimately the rejection and its argumentations are almost identical to the previous rejections which were overcome following the last two responses.

Being that the rejection is essentially identical to the previous rejections (which have already been overcome) and also the arguments (which were successful) will be almost the same (although in other words), the Examiner hopefully will appreciate and understand the nature of the claimed invention.

ARGUMENTS IN SUPPORT OF PATENTABILITY

The claimed invention is about a process which is suitable for the bulk manufacturing of raloxifene hydrochloride in a pure and crystalline form. It is a simplified process compared to those known from the prior art. While it may be true that the process recited in claim 26 (and the claims depending thereon) is similar (at least in its synthetic pathway) in its initial steps to US'684, it differs from known processes in its last steps d1) and d2).

The Examiner asserts that Alt US'684 differs from the claimed invention in the following respects:

(a) US'684 isolates the crude product 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene (VI) prior to converting it to the desired product (I), while the instant invention does not isolate (VI);

(b) the claimed invention recites a crystallization of the final product compared to Alt's acid-base work-up and chromatography purification; and,

(c) the claimed invention recites a process for preparing the HCl salt of compound (I) compared to the seemingly neutral form (free amine) disclosed in Alt.

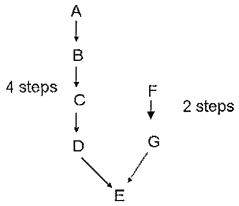
In the motivation for point (a) above, the Examiner, makes reference to Dorwald, stating that an organic chemist would be motivated to take the prior art of Alt '684 and reduce the step of isolation of 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene (VI) in order to achieve the final product (I) in greater yield and higher purity.

Applicants disagree with this statement. Dorwald refers to a synthetic strategy in the context of a synthesis design from a retrosynthetic point of view. This clearly indicates a synthetic strategy that individuates the starting material and renders the intermediates better suitable to achieve the target compound. The synthetic strategy individuates a pathway from the starting material to the final product passing through certain intermediates. A synthetic pathway is thus characterised by a certain number of chemical transformations which can involve the formation of intermediates in order to achieve the final product. The synthetic strategy is the sequence of chemical reactions for preparing a compound from a given starting material.

Thus, it should be noted that Dorwald's paragraph *"the shortest synthetic strategies which are likely to give rapid access to the target compound, ideally in high yield and purity"* is intended to be the shortest synthetic pathway in terms of the number of intermediates or chemical transformations.

It is evident that Dorwald's suggestion is a generic affirmation in synthetic chemistry. In fact, when choosing among two different pathways, for example one involving four (4) chemical transformations and the other involving two (2) chemical transformations, the shortest one, i.e. the one with only two (2) chemical reactions, seems to be preferable ideally, even if only in view of a mathematical calculation. As a matter of fact, by taking into account only the number of chemical transformations, it seems that a higher yield can be obtained as shown below:

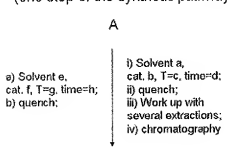
Synthetic pathways for
preparing compound E
starting from compound A or F



Four (4) steps: total yield of 65%, while two steps: 81% yield.

Ideally the shortest pathway seems to be more convenient because of a higher yield of Compound E as Dorwald teaches.

But also the single step should be considered in order to determine the yield and the purity.



The two possible procedures could result in:

i-iv : a lower yield but higher purity;

a-b : a higher yield but lower purity.

Thus, when choosing a procedure for a chemical reaction, the shortest path is not necessarily the best path to choose.

When looking for higher level of purity, one of ordinary skill in the art would probably try i-iv.

In the present case for the difference a) stated, the pathway of the claimed process is focused on the technical operations within a chemical reaction. The comparison with Alt document is therefore made by focusing on a single step. Accordingly, by starting from the Alt document, Dorwald's teaching goes in a ***completely opposite direction*** with respect to the claimed invention because it suggests to one of ordinary skill in the art to reduce the steps of a synthetic pathway and not to focus on the technical operations involved in a single step.

It is respectfully submitted that the Examiner may be confused between synthetic strategy and the sequence of technical operations to be performed within a single chemical reaction. What Dorwald teaches about synthetic strategies cannot be transposed directly to the sequence of technical operations to be performed within a single chemical reaction of a synthetic strategy. Technical operations within a chemical reaction (a step of a synthetic strategy) are, ***most definitely,*** other than a synthetic strategy. Given a chemical reaction, it is not true that the shortest sequence of technical operations would

assure the best yield and purity; in a chemical reaction the shortest number of operations/steps is not what assures the best result, while temperatures, times, solvents, reagents, work-up and purification protocols have to be selected carefully, on a case-by-case basis, for the same reaction which works well on a laboratory scale will not necessarily work as well on a bulk scale.

The Examiner has erroneously transposed the Dorwald's teaching related to the synthetic strategy (the least number of chemical reactions) to the sequence of technical operations to be performed within a single step of the synthetic strategy [i.e. at the end of chemical reaction of coupling between (V) and (IV), the non-isolation of the compound (VI)]. It is not obvious in an organic reaction that the omission of an operational step (i.e. simply the isolating of an intermediate) could turn out to be a successful accomplishment of the reaction in achieving greater yield and higher purity, contrary to the situation when operational steps (i.e. isolating steps) are omitted, impurities remain in the crude intermediate and such impurities are then carried forward in the following chemical transformations to the final product. In fact, isolation of a product usually involves a series of operations (such as filtration, washing and drying) that somehow purify the isolated compound. An isolation step cannot be omitted *a priori*, and to do so without compromising the purity of the final product, other modifications in the chemical reaction conditions and/or work-up are needed to allow for such an omission without compromising product purity.

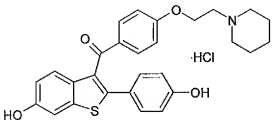
From the above arguments it should now be clear that the Dorwald's reference has been put forward improperly (because it was used out of its context) and the omission of the isolation step is, in fact, a non-obvious modification of Alt's procedure.

In argumentation of his points (b) and (c), the Examiner states that it would be obvious to convert the free-form compounds of formula (I) into its corresponding hydrochloride salt. This assertion is based on the combination of Alt and Gandolfi.

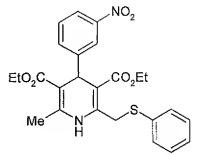
Most respectfully, this combination of documents by the Examiner is simply not understood and is traversed.

First of all, the Examiner states that the compounds disclosed in Gandolfi have structures similar to raloxifene. Applicants respectfully disagree since Gandolfi's

compounds manifestly have structures which are definitely different from the instant compound (I). Herein for the sake of clarity, the structural formulas of the instant compound (I) are set forth side-by-side with one of those compounds exemplified in Gandolfi (see Table column 20):



Instant compound (I)



One of Gandolfi's compounds

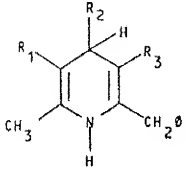
The structural diversity is evident and, quite frankly, Applicants fail to understand why Gandolfi has been cited. The statements in Gandolfi in column 2, lines 53-64 are absolutely generic. It is well-known in the pharmaceutical field that active organic compounds can be transformed into corresponding pharmaceutically acceptable salts. Such salts, depending on the pharmaceutically active ingredient and depending also on the combination with an acceptable acid can form a salt whose properties can be somehow changed (i.e. stability, solubility, taste, etc). The properties change from case-to-case and, in fact, for each new potential active ingredient in its drug development iter, each ingredient has to be tried with several possible pharmaceutically acceptable acids in order to find the one that can improve its properties.

The object of the claimed invention was not to provide a suitable pharmaceutically acceptable salt for ralofixene. Raloxifene hydrochloride is the active pharmaceutical ingredient (API) of a drug already on the market and this means that the suitability of the hydrochloride salt form of raloxifene was already known at the time of the claimed invention. Its suitability as an HCl salt was chosen (among many other possibilities) during its drug discovery iter.

Contrary to the foregoing, the object of the claimed invention is to provide an efficient (and suitable for bulk manufacturing) process for preparing raloxifene HCl with ***high purity***. Processes known in the art for preparing raloxifene hydrochloride are

unsatisfactory for performance and bulk scale and, furthermore, required long sequences of purification steps to achieve a pharmaceutical grade product. (See Alt column 12, lines 35-67 and column 13, lines 1-6.)

Gandolfi describes compounds of formula (I)



(I) (I)

wherein R1 is an alkoxycarbonyl group, acetyl, benzoyl, cyano, nitro or aminocarbonyl; R2 is an optionally substituted aryl or hetaryl group; R3 is an alkoxycarbonyl group; phi is a thio residue such as alkylthio, cycloalkylthio, arylthio, hetcroarylthio, aminoalkylthio, are described. The compounds of formula I are useful in human therapy as antihypertensive, antiulcer, antithrombotic, and antiischaemic agents. A synthetic process for the synthesis of compounds of formula (I) is also described. The formation of corresponding salts is not experimentally described but only generically in column 2, lines 53-64.

For the above reasons it is not understood how one of ordinary skill in the art would have arrived at the claimed process when Gandolfi is combined with Alt. Nowhere in Gandolfi is there any teaching or disclosure that this can be obtained directly and subsequently after a deprotection of the acetoxy group, i.e. by means of steps d1 and d2 of the claimed invention.

Steps d1 and d2 of the claimed invention are not simply a matter of minor and obvious experimental adjustments, but contrary to the view expressed by the Examiner are the fruit of intense and extensive experimentation with respect to each step of the process, which resulted in an overall synergistic method to obtain crystalline raloxifene

HCl directly from the last crude reaction mixture having a very high purity. Step d1 differs from the hydrolysis step described by Alt in that after the reaction there are neither washings, nor acid-base treatments, nor chromatography treatments. According to the claimed invention, the raloxifene which is obtained is already pure and it can be directly treated -- without the need of washings and chromatography -- with HCl to yield the hydrochloride salt. In the biphasic system (water/AcOEt), the raloxifene hydrochloride crystallizes (this is something entirely unexpected based upon Alt's teachings) and it can be isolated simply by filtration (i.e. centrifuging, which on a plant scale is much more convenient).

CONCLUSION

In view of the foregoing arguments, it should be clear to the Examiner that the claims clearly distinguish over the combination of art which he applied.

Since a ***prima facie*** case of obviousness in the sense of 35 USC § 103(a) has not been established by a preponderance of the evidence, withdrawal of the rejection is respectfully solicited.

The issuance of a Notice of Allowance is respectfully solicited.

Please charge any fees which may be due and which have not been submitted herewith to our Deposit Account No. 01-0035.

Respectfully submitted,

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